5-23-05

AF/1642

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF APPEALS AND INTERFERENCES

Application of: Pramod K. Srivastava	Confirmation No.: 8697
Serial No.: 09/657,722	Art Unit: 1642
Filed: September 8, 2000	Examiner: Christopher H. Yaen
For: PEPTIDES FROM STRESS PROTEIN-PEPTIDE COMPLEXES	Attorney Docket No: 8449-115-999

REPLY BRIEF UNDER 37 C.F.R. § 41.41

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In response to the Examiner's Answer, mailed March 23, 2005, and in accordance with 37 C.F.R. § 41.41, Appellant respectfully submits this Reply Brief and requests consideration of the remarks made herein. Appellant's Brief on Appeal was filed on December 6, 2004. A Request for Oral Hearing Under 37 C.F.R. § 41.47 is submitted herewith.

It is estimated that no fee is required for filing this Reply Brief. However, should the Patent Office determine otherwise, please charge the necessary fee to Jones Day Deposit Account No. 50-3013.

I. RESPONSE TO EXAMINER'S ARGUMENTS

A. The Rejection of Claims 19, 22-31 and 52-55 Under 35 U.S.C. § 112, First Paragraph, For Lack of Written Description

1. Claims 19, 22-31 and 52-55

Claims 19, 22-31 and 52-55 stand rejected under 35 U.S.C. § 112, first paragraph for lack of proper written description.

Appellant responds to each of the Examiner's arguments separately and in detail below.

The Examiner contends that the written description is not commensurate in scope with the claims because although the stress protein-peptide complexes can be determined and isolated by the methods of the present invention, the claims as currently recited "read on any protein fragment or polypeptide fragment that are [sic] derived from a tumor cell from which the complex was initially extracted" (see p. 4, 2nd par. of Examiner's Answer). The Examiner further contends that "because the specification has not described the structure and makeup of the peptides in the claimed composition, it [the composition] can be equivalent to any known composition wherein the composition comprises a peptide or protein fragment" (see p. 4, 2nd par. of Examiner's Answer).

Appellant submits that the Examiner's statement that the claims as currently recited read on any protein fragment or polypeptide fragment that is derived from a tumor cell from which the complex was initially extracted is erroneous. The currently appealed product-by-process claims recite a composition comprising a recovered population of peptides produced by a method comprising the steps of: (a) purifying the population of stress protein-peptide complexes from mammalian tumor cells, wherein the stress protein is noncovalently associated with the peptide in said complexes; (b) releasing the peptides from said population of complexes to produce a released population of peptides; and (c) recovering the released population of peptides (see, *e.g.*, presently appealed claim 19). By the very nature of the method recited in the claims, the peptides cannot read on any protein fragment or polypeptide fragment in the cell, because only peptides noncovalently associated with a stress protein within the cell are recovered. Moreover, the stress protein-peptide complexes, and consequently, the recovered population of peptides, are unique to the tumor cells of the mammal from which they were derived, *i.e.*, they reflect (are characteristic of) both the individual mammal and the tumor type from which they were derived. See, *e.g.*, p. 3, lines 2-

5 of the specification as filed, where it is disclosed that "human cancers, like cancers of experimental animals, are antigenically distinct." This statement is consistent with the observation that although mice vaccinated with their own inactivated cancer cells become immunized against subsequent challenges of live cancer cells, they still remain sensitive to challenges with other unrelated tumors (see, *e.g.*, p. 1, lines 24-31 of the specification as filed). This is also true for stress protein-peptide complexes, since, *e.g.*, stress protein-peptide complexes from a given tumor can immunize against that particular tumor and not an unrelated tumor (see, *e.g.*, Udono and Srivastava, 1993, *J. Exp. Med.* 178:1391-1396 (reference DU of record)). The population of peptides recovered from the stress protein-peptide complexes reflects not only what proteins are expressed by the cells from which they are recovered, but also what peptides are complexed to stress proteins in the cell.

Furthermore, the Examiner has not provided any evidence to support his statement that the claimed composition can be equivalent to any known composition wherein the composition comprises a peptide or protein fragment. To the contrary, since it is commonly known that different types of cells, and cells of different individuals, express and thus contain different populations of peptides, it is clear that the population of peptides recited in the claims differs for different cell types and for cell types from different individuals. For example, cells of the liver express and contain different populations of peptides compared to cells of the heart and other tissues. In the same respect, tumor cells express and contain different populations of peptides compared to non-tumor or non-malignant cells, since it is commonly known that tumors show distinct antigenicity (see, *e.g.*, pp. 1-2 of the specification as filed).

Moreover, the claimed composition cannot be deemed equivalent to any known composition wherein the composition comprises a peptide or protein fragment, because methods that can be used to dissociate peptides from the stress protein-peptide complexes are not selective with respect to the identity of particular peptides. For example, one could alter the conditions such that one may selectively release low affinity binding peptides or those which bind with higher affinity. However, there are no methods known to Appellant, presently, or at the time of filing, nor taught in the specification, that would allow selective dissociation of particular peptides from the stress protein-peptide complexes obtained from a cell. For example, although ATP or low pH can be used to dissociate peptides from stress protein-peptide complexes, they do not allow *selective* dissociation of particular peptides. Indeed, a proper reading of claim 19 would lead one of skill in the art to

conclude that the recovered population of peptides in the claimed composition is a heterogeneous population of peptides because methods available to the skilled artisan for releasing the peptides from the stress protein-peptide complexes are non-selective with respect to particular peptides. Appealed claim 19 recites:

A composition comprising a recovered population of peptides in admixture with a pharmaceutically acceptable non-toxic carrier, wherein said recovered population of peptides is produced by a method comprising the steps of:

(a) purifying a population of stress-protein-peptide complexes from mammalian tumor cells, wherein the stress protein is noncovalently associated with the peptide in said complexes;

(b) releasing the peptides from said population of complexes to produce a released population of peptides; and

(c) recovering the released population of peptides.

Upon reading the claim, one of skill in the art would understand that step (b) requires *releasing* the peptides from the population of stress protein-peptide complexes, and step (c) requires recovering the *released population of peptides* (emphasis added). Regarding step (b), as Appellant has explained above, there are no methods known to Appellant presently, or at the time of filing, nor taught in the specification, that would allow selective dissociation of particular peptides from the stress protein-peptide complexes. As such, the peptides released would have to be a heterogeneous population of peptides. This is supported by the findings of Liu and colleagues, who demonstrated that the peptide repertoire found to be associated with stress proteins is very diverse and heterogeneous (Liu *et al.*, "*De novo* identification of the ever-elusive gp96-associated peptides," Int'l Conf. on Heat Shock Proteins in Immune Response, Farmington, CT, October 6-9, 2002, Abstract, p. 31 (reference GE of record)). Liu and colleagues observed that several hundred peptides were found to be associated with gp96, a known stress protein. Moreover, they identified more than 20 peptides, among the several hundred peptides released, with "[n]o obvious consensus in the amino acid sequence or biophysical properties," *i.e.*, there were at least 20 different and unrelated peptides found to associate with gp96 (reference GE of record). Step (c) of the claim, the recovery step, requires that essentially the entire released population be recovered, since it specifies recovering "the released population of peptides," and <u>not</u> recovering "a <u>portion</u> of the released population of peptides." It is this recovered population of peptides resulting from step (c) that appears in the first line of claim 19, in admixture with a

pharmaceutically acceptable non-toxic carrier. Based on the clear language of the above steps of claim 19, the fact that the peptides associated with stress proteins inside a cell are a heterogeneous population, and that selective release of particular peptides from stress proteins does not occur under any known conditions, it is clear that the recovered population recited by the claim is a heterogeneous population and the claimed composition would not expected to be equivalent to any known composition comprising peptides, because methods that can be used to dissociate peptides from the stress protein-peptide complexes would be expected to result in a heterogeneous population of peptides that is unique to the cells from which the stress protein-peptide complexes were derived.

This conforms with the very object of the invention, which is to circumvent the need to identify individual immunogenic antigens of tumors from cancer patients (see, *e.g.*, page 3, lines 15-19 of the specification as filed), and to use the recovered population of released peptides for immunotherapy in patients suffering from cancer. As stated in the specification on page 3, line 33 to page 4, line 6, "[t]he method described herein does not require the isolation and characterization of specific antigenic determinants, and accordingly provides a more rapid approach for making and using immunogenic compositions effective in inhibiting the proliferation of specific predetermined tumors in mammals." Appellant respectfully points out that the Examiner has not come forward with any basis to support the existence of any dissociation methods selective for particular peptides in support of his contention.

The Examiner further argues that "a skilled artisan cannot determine from the disclosure what types of peptides are isolated from the HSP-peptide complex or its amino acid sequence. Moreover, the specification fails to characterize any of the peptides isolated from the HSP-peptide complex or provide any structural-functional relationship of the peptides or provide any common core structure to indicate to one of skill in the art that appellant was in possession of the time of filing" (see p. 6 of Examiner's Answer).

Appellant submits that contrary to the Examiner's statement, a structural-functional relationship has been provided. The structural-functional relationship shared among the peptides of the recovered population recited in the claims is their common ability to complex intracellularly to the specific type of stress protein molecule from which they were dissociated. Moreover, such stress protein-peptide complexes are unique not only to the particular tumor cell type from which they were derived, but also to the mammal (or mammalian cell line) from which the tumor cells were obtained. Furthermore, because of the

nature of the invention, Appellant has chosen to claim the product (*i.e.*, the recovered population of peptides) by means of a product-by-process claim. Appellant has discussed at length in Appellant's Brief on Appeal the requisite standard for product-by-process claims and why the presently appealed claims are proper (see, *e.g.*, pp. 4-5 of Appellant's Brief on Appeal, filed Dec. 6, 2004). As such, one of skill in the art would able to determine that at the time of filing, the Applicant was in possession of the claimed invention, thus satisfying the written description requirement.

The Examiner also contends that "because the population of peptides recovered during each round of purification would be different and distinct, and because the tumor cells from which the population of peptides have not been disclosed, one of skill in the art would not be able to determine which of the thousands if not millions of peptides extracted from the claimed process are recovered" (see p. 7 of Examiner's Answer).

Appellant submits that the Examiner's statement is unfounded, because, as discussed above, the claims require that essentially the entire released population of peptides be present in the claimed composition. Furthermore, Appellant has disclosed specific examples of tumors from which the stress-protein peptide complexes can be isolated (see, *e.g.*, pp. 14-15 which list numerous types of tumors to be used in the methods of the invention) with, in combination with the individual, would dictate the characteristic population of peptides recovered. Additionally, the determination or identification of the individual peptides is not necessary because the methodology recited in the claim does not require such characterization, since the population of peptides recovered from a stress protein-peptide complex for use in cancer immunotherapy is "tailor-made" for each individual being treated (see, *e.g.,* page 14, lines 1-11 of the specification as filed).

Further, the Examiner cites the Manual of Patent Examining Procedure Section (MPEP) Section 2113 and *In re Thorpe*, 777 F.2d 695, 698, 227 U.S.P.Q. 964, 966 (Fed. Cir. 1985), for the idea that "if the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior art product was made by a different process" (see p. 7 of Examiner's Answer). The Examiner contends that "[i]the instant case, the whole or partial structure of the peptide recovered using the claimed method cannot be determined, because no identifying characteristics have been taught and one of skill in the art would not be able to determine whether the recovered product is already within the public domain" (see p. 7 of Examiner's Answer). The Examiner further argues that "Applicant's reliance on *In re Luck* is misplaced, because the method *must*

define a structure in whole or in part," (italics added) and "because the process by which the product claimed does not define a definitive population of peptides either in whole or in part, one of skill in the art would not be able to determine that the applicant was in possession of the invention at the invention was made" (see pp. 7-8 of Examiner's Answer).

Appellant respectfully submits that the Examiner's argument is erroneous because, *inter alia*, the product of the process recited in the claim is distinct and nonobvious from prior art peptide populations, due to the characteristics imparted to the peptide population by the process by which it is made. Further, a product-by-process claim does not require that identifying characteristics of the product be specified in the claim (see, *e.g.*, *In re Luck*, 476 F.2d 650, 653, 177 U.S.P.Q. 523 (C.C.P.A. 1973). The recovered population of peptides is derived from cellular stress protein-peptide complexes, and thus is unique not only to the tumor cells from which the complexes were derived, but also to the individual (or cell line) from which the tumor cells were obtained.

Finally, the Examiner found unpersuasive Appellant's remarks that the instant invention provides a method for capturing a distinct antigenic profile of a given tumor for use in immunotherapy, and that the present invention circumvents the impractical and daunting task of identifying individual antigens associated with the HSP molecules. To support this contention, the Examiner cites *In re Gardner*, 57 C.C.P.A. 1207, 166 U.S.P.Q. 138, 141 (C.C.P.A. 1970) as support for the statement that "Law requires that the disclosure of an application shall inform those skilled in the art how to use applicant's alleged discovery, not how to find out how to use it for themselves" (see p. 8 of Examiner's Answer).

Appellant respectfully submits that the above alleged basis for the Examiner's rejection is improper because it is concerned with enablement, not written description. The opinion by the Court of Customs and Patent Appeals ("C.C.P.A.") in *In re Gardner* discussed an enablement rejection (see *In re Gardner*, 166 U.S.P.Q. at 141: "It behooves them, therefore to disclose how to use, as section 112 ordains, 'in such full, clear, concise, and exact terms as to enable any person skilled in the art...to ...use' their invention"). There, the C.C.P.A. affirmed the decision of the Board of Patent Appeals and Interferences to reject all claims for failing to comply with the requirements of 35 U.S.C. § 112, first paragraph. The claims at issue required the use of pharmaceutical compositions to alleviate depression. However, the C.C.P.A. concluded that the specification made no mention as to the recipient of the antidepressant drugs (*i.e.*, human or animal), and thus the range recited by the claims at issue (*i.e.*, from 10 mg to 450 mg) was "so great as to not be an enabling or how-to-use

disclosure as contemplated by the statute." *In re Gardner* at 141. Thus, Appellant submits that this is not a proper basis for a written description rejection, and that to Appellant's knowledge, there is no enablement rejection of record, nor any reasonable basis therefor.

In view of the foregoing, the Examiner's final rejection of claims 19, 22-31 and 52-55 for lack of proper written description under 35 U.S.C. § 112, first paragraph, is erroneous and should be reversed.

B. The Rejection of Claim 19 Under 35 U.S.C. § 102(b) as Anticipated by the '076 Patent

1. Claim 19

Claim 19 stands rejected as being anticipated under 35 U.S.C. § 102(b) by U.S. Patent No. 5,210,076, issued May 11, 1993, by Berliner et al. ('the '076 patent), as evidenced by Noessner et al., 2002, *The Journal of Immunology* 169:5424-5432 ("Noessner").

Appellant responds to each of the Examiner's arguments separately and in detail below.

As a basis for the anticipation rejection, the Examiner states that the '076 patent discloses "a tyrosinase protein wherein the said protein is found in a compound comprising a pharmaceutically acceptable carrier" (see page 4 of Examiner's Answer). "As evidenced by Noessner, tyrosinase is a peptide which can be associated with an HSP70 protein, thereby forming a complex" (see pp. 4-5 of Examiner's Answer). Thus, the Examiner contends that "because the claims are drawn to a product by process, and because the product being produced are [sic] already known, the process by which the product is made does not carry any patentable weight" (see p. 5 of Examiner's Answer).

Appellant submits that the Examiner's argument is erroneous. Appellant respectfully reminds the Examiner that the legal standard for anticipation under 35 U.S.C. § 102 (b) is one of strict identity. A claim is anticipated only if each and every element set forth in the claim is found, either expressly or inherently, in a single prior art reference. *Verdegaal Bros., Inc. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051 (Fed. Cir. 1987); *Schering Corp. v. Geneva Pharmaceuticals, Inc.*, 339 F.3d 1373, 1377, 67 U.S.P.Q.2d 1664 (Fed. Cir. 2003); and *Atlas Powder Co. v. IRECO, Inc.*,190 F.3d 1342, 1347, 51 U.S.P.Q.2d 1943 (Fed. Cir. 1999). In other words, there must be no difference between the claimed invention and the reference disclosure as viewed by a person of ordinary

skill in the field of the invention. *Scripps Clinic & Research Foundation v. Genentech, Inc.*, 927 F.2d 1565, 1576, 18 U.S.P.Q.2d 1896 (Fed. Cir. 1991).

Once again, citing MPEP § 2113 and *In re Thorpe*, 222 F.2d at 698, 227 U.S.P.Q. at 966, the Examiner contends that "even though the product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior art product was made by a different process" (see p. 9 of Examiner's Answer). Further, the Examiner cites the MPEP and *In re Garnero*, 412, F.2d 276, 279, 162 U.S.P.Q. 221, 223 (C.C.P.A. 1979), to argue that "[t]he structure implied by the process steps should be considered when assessing the patentability of product-by-process claims over the prior art, especially where the product can only be defined by the process steps by which the product is made, or where the manufacturing process steps would be expected to impart distinctive structural characteristics to the final product" (see p. 10 of Examiner's Answer). The Examiner argues that in the present case, the specification has not provided any indication that the method of producing the population of peptides imparts any structurally distinct aspect.

As discussed above, Appellant submits that a product-by-process claim need not recite identifying or structural characteristics of the product. Rather, the identifying characteristics of the product are a result of the process by which it is made (see, *e.g.*, *In re Luck*, 476 F.2d 650, 653, 177 U.S.P.Q. 523 (C.C.P.A. 1973)). The recovered population of peptides are derived from cellular stress protein-peptide complexes, and thus are unique not only to the type of tumor cells from which they were derived, but also to the individual (or cell line) from which the tumor cells were obtained.

Moreover, the Examiner argues that the claims do not specifically limit the peptide population to heterogeneous populations and therefore the peptide taught by the '076 patent (*i.e.*, tyrosinase), as evidenced by Noessner, anticipates the population of peptides claimed because tyrosinase can be a peptide potentially found in the population.

Appellant respectfully disagrees with the Examiner's contention. Although the claims do not explicitly recite a "heterogeneous" population, the common and ordinary meaning of a population of peptides (plural) is that the population comprises distinct peptides (thus, the difference in meaning between a population of "peptides" (plural) and a population of "a peptide" (singular)). As demonstrated by Liu and colleagues, the population of peptides

found to be associated with gp96 numbered in the hundreds, with at least 20 peptides found to "have no obvious consensus in the amino acid sequence or biophysical properties" (reference GE of record). Thus, the Examiner's tortuous construction of the word "population" is not only inconsistent with the common and ordinary meaning of the word, but is inconsistent with the population of peptides that associate with stress proteins, as demonstrated by Liu *et al.*

Furthermore, as discussed above in more detail, a proper reading of claim 19 would lead one of skill in the art to conclude that the recovered population of peptides in the claimed composition is a heterogeneous population of peptides because methods available to the skilled artisan for releasing the peptides from the stress protein-peptide complexes are non-selective with respect to particular peptides (*see also* reference GE of record). Step (c) of the claim, the recovery step, requires that essentially the entire released population be recovered, since it specifies recovering "the released population of peptides," and not recovering "a portion of the released population of peptides." It is this recovered population of peptides resulting from step (c) that appears in the first line of claim 19, in admixture with a pharmaceutically acceptable non-toxic carrier. Based on the clear language of the above steps, the fact that the peptides associated with stress proteins inside a cell are a heterogeneous population, and that selective release of particular peptides from stress proteins does occur not under any known conditions, it is clear that the recovered population recited by the claim is a heterogeneous population that cannot be anticipated by the '076 patent.

Appellant finally notes the Examiner's reference to a lack of utility of the invention (see p. 10 of Examiner's Answer). Appellant respectfully submits that to Appellant's knowledge, there is no lack of utility rejection in the record, nor any reasonable basis therefor.

C. Conclusion

For all of the reasons set forth above, Appellant respectfully requests that all of the rejections of the claims on appeal be reversed.

Respectfully submitted,

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